REMARKS

Claims 1-52 are pending in the application. Claims 10-41 and 46-52 have been withdrawn by the Examiner as directed to a non-elected invention. Reconsideration of the claims in view of the following Remarks is requested.

I. The Specification Fully Enables the Present Claims

Claims 1-9 and 46-52 were rejected under 35 U.S.C. 112, first paragraph, for alleged lack of enablement. Applicants traverse this rejection.

Applicants note that the Examiner "has the initial burden to establish a reasonable basis to question the enablement provided for the claimed invention." *MPEP 2164.04.* A finding that further experimentation is necessary to practice an invention is insufficient to question the enablement of the claims. "The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation." *MPEP 2164.01.*

Additionally, "[a]s long as the specification discloses at least one method for making and using the claimed invention that bears a reasonable correlation to the entire scope of the claim, then the enablement requirement of 35 U.S.C. 112 is satisfied." *MPEP 2164.01(b).* Indeed, "[a] specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must** be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support" (emphasis added). *MPEP 2164.04.*

Moreover, compliance with the enablement requirement "does not turn on whether an example is disclosed," and an "applicant need not have actually reduced the invention to practice prior to filing." *MPEP 2164.02.* Claims can be enabled by disclosure of data from *in vitro* or *in vivo* animal models, if there is a reasonable correlation between the model and the claimed *in vivo* activity; a "rigorous or invariable" correlation is not required. MPEP 2163.02.

The claims are directed to methods of treating insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle, comprising administering a Dkk-1 antagonist. In the present case, therefore, the claims satisfy the enablement requirement if the disclosure

enables the use as claimed, i.e., the treatment of insulin resistance or hypoinsulinemia, or methods of repairing or regenerating muscle. Applicants submit that, in light of the foregoing standards, the claims are clearly enabled.

Insulin resistance is a state characterized by normal or elevated blood glucose levels that persist in the presence of normal or elevated levels of insulin, such that basal or insulin-stimulated glycogen synthesis, or both, are lowered to subnormal levels (page 2, lines 26-30 of the specification). The present specification provides data demonstrating that muscle cells treated with Dkk-1 exhibited insulin resistance (Example 1; page 50, lines 18-19). The specification also discloses that administration of Dkk-1 lowered levels of basal and insulin-stimulated glucose uptake in L6 muscle cells by inhibiting Akt, a known key intermediate in the insulin-signaling pathway (page 50, line 30 through page 51, line 2). Therefore, the Applicants have provided evidence directly linking the activity of Dkk-1 to the reduced glucose uptake characteristic of insulin resistance.

The specification also provides *in vivo* data demonstrating that intravenous injection of recombinant Dkk-1 in mice resulted in impaired glucose tolerance and reduced insulin production (page 48, lines 13-24 and Figs. 11A and 11B). The Applicants have also disclosed that intravenous injection of Dkk-1 in mice altered expression of multiple muscle-specific genes that were consistent with results seen in L6 muscle cells, providing evidence that Dkk-1 affects muscle differentiation both *in vitro* and *in vivo* (page 48, lines 25-36).

Applicants reiterate that, regarding the correlation of *in vitro* or *in vivo* animal models to the scope of the claims, a "rigorous or invariable exact requirement is not required" to meet the enablement standard. *MPEP 2163.02.* Rather, the correlation need only be reasonable. Applicants respectfully submit that the presently disclosed data reasonably correlates with the claim scope. Specifically, in light of the disclosure of:

1) *in vitro* data demonstrating the ability of Dkk-1 to reduce glucose uptake, a key feature of insulin resistance, as well as to promote muscle differentiation; and

2) *in vivo* data demonstrating that injection of recombinant Dkk-1 in mice resulted in impaired glucose tolerance and reduced insulin production,

Applicants submit that one of ordinary skill could have reasonably predicted at the effective filing date of this application that the claimed methods of administering Dkk-1 antagonists could repair or regenerate muscle, as well as increase basal and insulin-stimulated glucose uptake.

Applicants respectfully disagree that the disclosure reveals unpredictable effects of Dkk-1 that render the claims non-enabled. As discussed above, the specification discloses that in an animal model, Dkk-1 impaired glucose tolerance and reduced insulin production *in vivo*. Applicants reiterate that it is unnecessary to reduce an invention to practice in order to enable the claims, and that disclosure of data from an *in vivo* animal model can provide enablement if there is a reasonable correlation between the model and the claimed activity. For the reasons discussed above, Applicants submit the disclosed *in vivo* data does reasonably correlate with the scope of the claims.

Applicants submit the present claims are fully enabled, and withdrawal of the rejection is respectfully requested.

II. The claims do not lack enablement for lack of safety.

The Examiner also contends, however, that the present invention would require undue experimentation to practice as claimed, because one of skill in the art would recognize that administration of a Dkk-1 antagonist could exacerbate or induce cancer. Applicants respectfully disagree.

A. Applicants respectfully submit the rejection of the claims for alleged lack of safety is improper.

Applicants note the *MPEP* states that one "need not demonstrate that the invention is completely safe" to satisfy the enablement requirement. *MPEP 2164.01(c)*. The *MPEP* advises that the safety considerations taken into account by a regulatory body such as the FDA are "different from those made by the PTO in determining whether a claim is enabled." *MPEP 2164.05* (citing *Scott v. Finney*, 34 F.3d 1058, 1063 (Fed. Cir. 1994)("Testing for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]")). *Id.* Consequently, in light of the *MPEP's* statements that satisfaction of the enablement requirement does not require a showing of complete safety, Applicants respectfully submit that the enablement rejection is improper.

To the extent that a rejection based upon safety considerations is warranted, however, Applicants submit that such a rejection is properly made under 35 U.S.C. 101 rather than 35 U.S.C. 112, first paragraph. Indeed, *MPEP § 2164.06(a) III.*, rather than discussing safety considerations of drugs in an enablement context, instead refers the reader to the utility discussion of *MPEP 2107-2107.03*. This discussion delineates the limited nature of the USPTO's ability to reject claims due to safety concerns.

Specifically, *MPEP 2107.III.* discusses inventions directed to treating human or animal disorders, and notes that

> "[t]he Federal Circuit has reiterated that therapeutic utility sufficient under the patent laws is not to be confused with the requirements of the FDA with regard to safety and efficacy of drugs to marketed in the United States . . . Office personnel should not construe 35 U.S.C. 101 . . . to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans."

Similarly, *MPEP 2107.03* asserts that

> "[t]he Office must confine its review of patent applications to the statutory requirements of the patent law. Other agencies of the government have been assigned the responsibility of ensuring conformance to standards established by statute for the advertisement, use, sale or distribution of drugs. The FDA pursues a two-prong test to provide approval for testing. Under that test, a sponsor must show that the investigation does not pose an unreasonable and significant risk of illness or injury and that there is an acceptable rationale for the study . . . it is improper for Office personnel to request evidence of safety in the treatment of humans, or regarding the degree of effectiveness" (emphasis in the original).

The *MPEP* provides multiple citations to case law supporting its admonitions against safety-based claim rejections. *Id.* The Examiner's attention is respectfully directed to one of these cases, *In re Anthony*, 162 USPQ 594 (CCPA 1969), involving claims directed to an antidepressant. The FDA had suspended a New Drug Application (NDA) for the antidepressant, stating that clinical experience showed the compound was "unsafe for use under the conditions of use upon the basis of which the application became effective." *Id.* at 600.

In spite of the FDA's conclusion, the court reversed the Examiner's rejection of the claims under 35 U.S.C. 101 for lack of safety. The court stated that "the patent statutes do not establish

"safety" as a criterion for patentability of any of the statutory classes of patentable subject matter." *Id.* at 603. The court did acknowledge that

> "[n]o one, we suppose, would seriously maintain that, as a matter of policy, a composition unsafe for use by reason of extreme toxicity to the point of immediate death under *all* conditions of its sole contemplated use in treating disease of the human organism would nevertheless be useful within the meaning of the patent laws" (emphasis in the original). *Id.*

The court found, however, that the claimed compound did not run afoul of the foregoing toxicity standard, and concluded that "Congress has given the responsibility to the FDA, not to the Patent Office, to determine in the first instance whether drugs are sufficiently safe for use." *Id. at 604.*

The Examiner's attention is also respectfully directed to another case cited by the *MPEP*, *In re Watson*, 186 USPQ 11 (CCPA 1973), involving claims directed to germicide compositions that non-selectively kill bacteria to improve oral hygiene. The Examiner rejected the claims under both 35 U.S.C. 101 and 35 U.S.C. 112, first paragraph, for alleged lack of safety, and for failure to demonstrate that "the indiscriminate destruction of bacteria" would be useful. *Id.* at 14. The Examiner based the rejection upon references said to show that "those skilled in the art would not consider . . . appellant's compositions safe for human use," and upon the Examiner's conclusion that use of the compositions could increase levels of a "death-producing" organism in the mouth. *Id.*

The CCPA reversed the rejection by citing the portions of *In re Anthony* quoted above. *Id.* at 19. The court asserted that "in the safety of pharmaceuticals Congress has given primary administrative jurisdiction to federal agencies other than the PTO," and concluded that the evidence of record failed to establish even a *prima facie* case for lack of safety under 35 U.S.C. 101. *Id.* at 20. Significantly, the court held that the 35 U.S.C. 112, first paragraph rejection stood or fell with the utility rejection, and therefore was also improper. *Id.*

Applicants respectfully submit that the present claims are enabled in light of the foregoing standards developed by the courts and discussed by the *MPEP*. The case law shows that issues of safety are not the province of the USPTO, unless a composition is completely lacking utility as a result of being "unsafe for use by reason of extreme toxicity to the point of immediate death under *all* conditions of its sole contemplated use in treating disease of the human organism." The case law, which has not been reversed or altered by the CAFC,

demonstrates that even an FDA finding that a claimed compound is unsafe for its contemplated use is insufficient by itself to sustain an enablement rejection.

At the very least, Applicants respectfully submit there is no persuasive evidence of record that administration of a Dkk-1 antagonist is unsafe, let alone any evidence that such administration is extremely toxic to the point of immediate death under all conditions of its contemplated use. The Applicants respectfully disagree that, in light of this toxicity standard, the claims can be rendered non-enabled because cancer is considered "more than a mere undesirable side effect" of a treatment for insulin resistance.

Applicants also submit it was well known in the art that some forms of insulin resistance can cause serious long-term complications such as atheromatous disease, neuropathy, nephropathy, retinopathy, and peripheral vascular disease. Applicants also submit it is known that even minimal glucose intolerance is associated with an increased risk of cardiovascular mortality. In light of the seriousness of these complications, the evidence does not clearly show that the benefits of the claimed methods are always or almost always outweighed by the alleged risks. Moreover, Applicants submit that the evidence of risk cited by the Examiner is not persuasive, as discussed below.

B. The evidence does not demonstrate that the claimed methods are unsafe.

Even assuming for the sake of argument that sufficient evidence of safety concerns could provide a reasonable basis to question enablement, Applicants respectfully submit that the evidence of record is insufficient to provide such a basis.

As an initial matter, Applicants note that of the eight references cited by the Examiner as supporting the role of Dkk-1 antagonists in causing or exacerbating cancer, seven post-date the filing date of the application. "In general, the examiner should not use post-filing date references to demonstrate that the patent is nonenabling." *MPEP 2164.05(a)*. Applicants respectfully submit, therefore, that these references are not relevant to the issue of enablement of the present claims.

Applicants also submit that the remaining reference, Wang et al, is insufficient to establish that the present invention is unsafe. Wang et al. asserts that Dkk-1 may mediate p53 tumor suppression by antagonizing the Wnt pathway, and states that p53 can induce Dkk-1 (Abstract). Nevertheless, Wang et al. discloses that administration of Dkk-1 had no effect on the

growth rates of either of two cancer cell lines (page 1847, first paragraph). Applicants submit that, at best, Wang et al. provides conflicting evidence concerning the effect of Dkk-1 on proliferation of cancerous cells, and is therefore insufficient to provide a reasonable basis to question the safety of the claims.

Moreover, Applicants submit that even if use of the remaining 7 references is considered proper, the combined teachings of these references also fail to establish a reasonable basis to question the safety of the claimed methods. As was discussed above, the present invention provides data clearly demonstrating that Dkk-1 administration can stimulate glucose uptake, and causes impaired glucose tolerance *in vivo*. Therefore, the Applicants have provided direct evidence linking Dkk-1 to the features of insulin resistance. In contrast, none of the 7 remaining references provide direct evidence that Dkk-1 activity prevents carcinogenesis.

Uematsu et al., for example, discloses that Dvl-3 is overexpressed in already cancerous NSCLC cell lines (Abstract), but does not provide any direct evidence that Dkk-1 suppression induces cancerous proliferation. The experiments conducted by Uematsu et al. were focused on the role of Dvl-3, and did not involve Dkk-1.

Chen et al. discloses that overexpression of the oncoprotein SKI correlates with progression of human melanoma, and that SKI activates the Wnt pathway (Abstract). This reference is not directed to Dkk-1 either, and does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

Gonzales-Sancho et al. discloses that Dkk-1 is downregulated in colon tumors (page 1101, second paragraph). This reference hypothesizes that "Dkk-1 may act as a tumor suppressor gene in colon cancer," but admits that "[i]t remains to be determined whether extracellular DKK-1 exerts a suppressive effect, given that the pathway is disregulated in this neoplasia as a result of APC or β-catenin mutations that disconnect the downstream cascade from the Wnt receptors" (emphasis added). *Id.* Moreover, the authors note that DKK-1 is overexpressed in some other cancers, including human hepatic blastomas and wilms tumors. *Id.* While this reference hypothesizes that Dkk-1 possesses tumor-suppressive activity that is lost in cancerous colon cells, the disclosed conflicting pattern of Dkk-1 overexpression and underexpression seen among various cancers renders this reference ambiguous. Applicants

respectfully submit that Gonzales-Sancho et al. is insufficient to provide a reasonable basis for questioning the enablement of the claims.

Lee et al. discloses that Wnt antagonists, including Dkk-1, were known to be downregulated in a variety of cancers, and states that recent evidence shows restoration of the Wnt antagonists may have proapoptotic effects in tumor cells (p. 1247, first full paragraph). Lee et al. does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis in healthy cells.

The Le Floch et al. abstract asserts that "inappropriate" activation of the Wnt pathway plays a "critical role at early stages in a variety of human cancers," but discloses that Dvl-2, an activator of the Wnt pathway, "did not alter cell invasion into type I collagen." This abstract does not discuss Dkk-1 at all, and does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

Miyoshi et al. discloses that mammary epithelium from transgenic mice expressing certain activating molecules of the Wnt pathway can develop glandular tumors and squamous differentiation (Abstract). Dkk-1, however, is a Wnt suppressor, not a Wnt activator, and therefore was not tested by Miyoshi et al. Miyoshi et al. does not provide any direct evidence that Dkk-1 activity prevents carcinogenesis.

The Behrens et al. abstract states that Wnt signaling is a key pathway in cancer. This abstract does not provide any direct evidence, however, showing that Dkk-1 activity prevents carcinogenesis.

For the foregoing reasons, Applicants respectfully submit the cited references fail to provide persuasive evidence that the claimed methods are unsafe under any circumstance, let alone all circumstances. Withdrawal of the enablement rejection is therefore respectfully requested.

III. The Applicants have successfully rebutted any reasonable basis to question enablement.

As stated above, Applicants respectfully submit there is no reasonable basis to question the enablement of the claims. Even if one assumes the existence of a reasonable basis for the sake of argument, however, Applicants have successfully overcome the rejection by presenting

"persuasive arguments . . . that one skilled in the art would be able to make and use the claimed invention using the application as a guide," as required by *MPEP 2164.05*. To rebut a *prima facie* case of enablement,"[t]he evidence provided by applicant need not be conclusive but merely convincing to one skilled in the art (emphases in the original). *Id.*

In the present case, Applicants have provided convincing evidence that one of skill would know how to make and use the claimed invention. The Applicants respectfully disagree that one of skill in the art would conclude that downregulation of Dkk-1 is unwise. Indeed, one of skill in the art would recognize that downregulation of Dkk-1 may be useful in cancer therapies. Applicants submitted with the previous Response a reference by Tian et al (*NEJM* 2003; 349:2483-2494). Relying on citations to pre-filing-date references dating from 1986 to 1992, Tian et al. states that lung, breast, prostate cancer, and multiple myeloma were known to cause osteoblastic or osteolytic lesions in bone, and that these lesions are associated with decreased number and function of osteoblasts (first full paragraph). Citing to the pre-filing-date reference Cadigan et al. (*Genes Dev* 1997;11:3286-3305), Tian et al. further notes that the Wnt signaling pathway was known to be important for the growth and differentiation of osteoblasts. *Id.* In light of these teachings of the prior art, Tian et al. proceeded to study patterns of gene expression in myeloma cells, and disclosed that "[t]he production of DKK1, an inhibitor of osteoblast differentiation, by myeloma cells is associated with the presence of lytic bone lesions in patients with multiple myeloma." Furthermore, the present specification discloses that Dkk-1 stimulates the Wnt signaling pathway, and that antagonists of Dkk-1 are therefore useful in antagonizing Wnt signaling.

The Applicants reiterate that evidence rebutting a reasonable basis to question enablement need not be conclusive, but merely convincing to one skilled in the art.
In light of the knowledge in the art discussed above and the teachings of the specification, the Applicants submit that one of skill in the art at the time of the present invention would have reasonably predicted that the use of Dkk-1 antagonists to stimulate the Wnt signaling pathway could be useful in therapy.

The Applicants also submitted with the previous Response a post-filing-date media article from *Reuters Health* (December 24, 2003) that discusses the findings of Tian et al. Applicants note that although post-filing-date evidence cannot render an insufficient disclosure